THE PREPARATION OF AMINO ACIDS FROM 3,6-*bis*-(β-CHLOROETHYL)-2,5-DIKETOPIPERAZINE

BY

MAX EUGENE CHIDDIX

B. Ed., Illinois State Normal University, 1940
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Introduction

3,6-*bis*-(β-Chloroethyl)-2,5-diketopiperazine (I) recently has been made available as an intermediate in a synthesis of *dl*-methionine.[1] Conversion of the substance to methionine requires only replacement of the chlorine atoms by methylthiol groups, and hydrolysis of the resulting methionine anhydride. It should be possible to prepare the anhydrides of a variety of α-amino acids by replacement of the chlorine atoms by other groups. Still others might be prepared by addition of appropriate reagents to the unsaturated compound (II) formed by dehydrohalogenation of the dichloro compound (I). The present work was undertaken to test the use of 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine in such syntheses.

Discussion of Results

The unsaturated compound, 3,6-divinyl-2,5-diketopiperazine (II), m.p. 192.5° (cor.), was prepared in 62 per cent yield by heating the dichloride (I) with sodium hydroxide in ethanol. The hydrolysis of the divinyl compound (II) with hydrochloric acid produced α-amino-γ-butyrolactone hydrochloride (III).[2] This same lactone (III) was produced when the dichloride (I) was hydrolyzed with concentrated hydrochloric acid.

The addition of hydrogen chloride to the double bonds of the divinyl compound (II) in glacial acetic acid solution produced a dichloride (IV), m.p. 233-234° (cor.), which had the same structure as the dichloride (I). The yield was 60 per cent. The preparation of methionine anhydride, methionine, and benzoyl methionine[3] from the dichloride (IV) established its structure. 3,6-*bis*-(β-Bromoethyl)-2,5-diketopiperazine (V), m.p. 221-222° (cor.), was prepared in 53 per cent yield

by adding hydrogen bromide to the unsaturated compound (II), and it was converted to methionine anhydride. This non-Markownikoff addition of hydrogen chloride and hydrogen bromide might be explained by the polarization of the double bonds of compound (II) by the proximity of the positive charges of the salt formed from the halogen acid and the diketopiperazine ring.

A dithiol compound (VI), m.p. 185-186° (cor.), resulted from the reaction of hydrogen sulfide with the divinyl compound (II) in ethanol solution in the presence of glacial acetic acid. The yield was 56 per cent. The hydrolysis of this product with concentrated hydrochloric acid to homocysteine thiolactone hydrochloride[4] in good yield is strong evidence that the dithiol compound (VI) is homocysteine anhydride. However, du Vigneaud[5] gives the melting points of 237° and 208° for the diasterioisomeric forms of homocysteine anhydride. The methylated derivative of compound (II), obtained in low yield, was isomeric with the known methionine anhydride.[1] Bromine reacted with the unsaturated compound (II) in glacial acetic acid to produce a yellow perbromide, m.p. 112-115° (cor.), which was converted to a white compound (VII), m.p. 221-222° (cor.), by the action of sodium sulfite. The analysis indicated that the compound (VII) was a dibromide. The reaction of chlorine with the unsaturated compound (II) produced a dichloride, m.p. 232-234° (cor.). Unsuccessful attempts were made to cause the addition of sulfuric acid, ethanol, monoperphthalic acid, methyl mercaptan, and benzyl mercaptan to the double bonds of the divinyl compound (II).

The reaction of the dichloride (I) with morpholine resulted in a 45 per cent yield of 3,6-*bis*-(β-N-morpholinoethyl)-2,5-diketopiperazine, m.p. 229-232° (cor.). An analogous compound, m.p. 242-243° (cor.), was prepared from piperidine and the dichloride (I).

The dichloride (I) reacted with potassium thiocyanate in acetone to produce 3,6-*bis*-(β-thiocyanoethyl)-2,5-diketopiperazine (IX), m.p. 207-208° (cor.), in 15 per cent yield.

The reaction of salts of acetoxime, benzohydroxamic acid, and hydroxylamine disulfonic acid with the chloride (I) and the corresponding iodine compound (VIII) produced the unsaturated compound (II). The substitution of nitrile groups for the halide atoms of compounds (I) and (VIII) was unsuccessfully attempted using potassium cyanide, sodium cyanide, and silver cyanide. The alkylation of acetoacetic ester with the dichloride (I) or the analogous iodine compound (VIII) was attempted without success.

References

1. Snyder, Andreen, Cannon, and Peters, J. Am. Chem. Soc., **64**, 2082 (1942).
2. Feofilaktov and Onishchenko, J. Gen. Chem. (U.S.S.R.), **9**, 304, 314 (1939); C.A., **34**, 378 (1940).
3. Windus and Marvel, J. Am. Chem. Soc., **53**, 3490 (1931).
4. Riegel and du Vigneaud, J. Biol. Chem., **112**, 149 (1935-1936).
5. du Vigneaud, **ibid.**, **126**, 217 (1938).

VITA

The author was born in Palestine, Illinois, on April 13, 1918. He graduated from the Normal Community High School, Normal, Illinois, in June 1936. He attended Illinois State Normal University, where he was granted the Bachelor of Education degree in June 1940. In September 1940 he entered the Graduate School of the University of Illinois. There he held a University Scholarship during the academic year 1940-1941, a teaching assistantship during 1941-1942, and a University Fellowship during 1942-1943.

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